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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/736,902
Filing Date: December 17, 2003
Appellant(s): BROWN ET AL.

Stephen M. Roylance
Reg. No. 31,296
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 25 April 2008 appealing from the Office action mailed 23 November 2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

Examiner notes for co-pending and commonly assigned Application No. 10/798,884, a Notice of Appeal was filed on February 19, 2008 and an Appeal Brief was filed on April 21, 2008 and supplemental Appeal Briefs were also filed on September 11, 2009 and October 20, 2008.

Examiner also notes that for co-pending Application No. 11/102,725, a Notice of Appeal was filed on October 6, 2008 and an Appeal Brief was filed on December 8, 2008.

Examiner also notes that for co-pending Application No. 11/115,293, a Notice of Appeal was filed on August 04, 2008 and an Appeal Brief was filed on November 05, 2008.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,699,502	FANARA et al.	3-2004
4,650,807	FINDLAY et al.	3-1987
5,445,829	PARADISSIS et al.	8-1995

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

- (A) Claims 1-24, 27-38 and 68-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fanara *et al.* (U.S. Patent No. 6,699,502) in view of Findlay *et al.* (U.S. Patent No. 4,650,807).

- (B) Claims 1-24, 27-38 and 68-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fanara *et al.* (U.S. Patent No. 6,699,502) in view of Paradissis *et al.* (U.S. Patent No. 5,445,829).

- Claims 1-24, 27-38 and 68-74 have also been rejected under the non-statutory doctrine of obviousness-type double patenting as allegedly being unpatentable over claims of co-pending Application Nos. 10/798,884, 10/910,806, 10/939,351, 11/012,267, 11/115,321, 11/102,725, 11/102,726 and 11/115,293. The provisional double patenting rejections have not been reproduced or presented in this Appeal.

* * * * *

- **(A) Claims 1-24, 27-38 and 68-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fanara *et al.* (U.S. Patent No. 6,699,502) in view of Findlay *et al.* (U.S. Patent No. 4,650,807).**

The instant invention is drawn to a pharmaceutical dosage form which comprises (a) a first drug which is at least one of promethazine and a pharmaceutically acceptable salt thereof and (b) at least one second drug, wherein the dosage form provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug.

Fanara *et al.* ('502) teach oral pharmaceutical compositions for controlled release of active substances, whereby the compositions include multi-layered formulations. The compositions can be administered in a few daily doses, ideally in a single daily dose (see column 1, lines 5-13 and Abstract). The release of active substances during oral administration can be controlled by means of matrix-type pharmaceutical compositions (col. 1, lines 14-16).

According to Fanara, it is increasingly therapeutically advantageous to be able to simultaneously administer by the oral route an active substance released immediately after administration, and the same or a second active substance released gradually and regularly after administration. In the case where an active substance is released immediately and another active substance is released gradually, this makes it possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles (col. 2, lines 36-50).

The compositions allow regular and continuous release of active substances over periods of at least 12 hours (col. 3, lines 28-31).

The controlled release compositions can be used in combination with an immediate release pharmaceutical composition for the same or for another active substance, in a single unit intended to be administered orally (col. 2, lines 32-37).

Suitable active substances disclosed include antihistamines, analgesics, antitussives and the like (col. 4, lines 57-58). Specific active substances taught include decongestants, such as pseudoephedrine, phenylepherine, phenylpropanolamine and antitussives such as hydrocodone, codeine, morphine, their optimal isomers or pharmaceutically acceptable salts (col. 4, lines 58-67).

The pharmaceutical compositions are provided in the form of tablets, of which bi-layered and multi-layered tablets are also included (col. 5, line 15 – col. 6, line 25).

The Examples at columns 6-18 demonstrate various layered controlled release pharmaceutical compositions of the invention. For instance, Example 7 at column 12, demonstrates a double-layered tablet comprising hydrocodone bitartrate. The double layered-tablets contained 15 mg doses of hydrocodone consisting of a controlled-release layer containing a 10 mg dose of hydrocodone and an immediate-release layer containing a 15 mg dose of hydrocodone. The results showed that 35% of hydrocodone was already released after 1 hour, which corresponds to the hydrocodone content in the immediate release layer (33.3% of the total dose). The release of the hydrocodone continued gradually and regularly (col. 12, line 24 – col. 13, line 26).

With respect to the instant claim limitation of the "dosage form providing a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70% of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug", it is the position of the Examiner that the Fanara reference meets these claim limitations. The Fanara reference explicitly recognizes and teaches simultaneous administration of multiple active agents whereby it is possible to combine therapeutic effects of active substances having very different pharmacokinetic profiles. Thus, the Fanara reference teaches an objective similar to that being claimed by Applicant.

With regards to the plasma half-lives claimed, it is noted that the Fanara reference teaches similar active ingredients as claimed and thus, the plasma half-lives would be expected to be the same as that claimed herein by Applicant.

Regarding the limitation of the 'tablet comprising a matrix with the first drug and particles which comprise the second drug', the Examiner points out that Fanara teaches the use of layered, both bi-layered and multi-layered tablets and thus, this limitation is also met by the primary reference.

Fanara *et al.* teach antihistamines (col. 4, line 58). Fanara et al. do not teach the antihistamines promethazine and chlorpheniramine and do not teach the antitussive-expectorant, guaifenesin.

Findlay *et al.* ('807) teach antihistaminic compositions, which can be in the form of tablets (col. 1, lines 6-25); (col. 5, lines 33-50). Suitable antihistamines taught include *pheniramines and promethazine* (col. 1, lines 26-31). Findlay *et al.* teach that the active compound may be formulated with a sympathomimetic agent such as decongestants (pseudoephedrine, phenylpropanolamine), an antitussive (i.e., codeine), an analgesic, anti-inflammatory or an antitussive-expectorant such as *guaifenesin* (col. 5, lines 1-21). The compositions are free from sedative effects and have little or no anticholinergic effects (Abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the suitable antihistamines and expectorants taught by Findlay *et al.* within the formulations of Fanara *et al.* One of ordinary skill in the art would be motivated to do so with a reasonable expectation of success because Findlay et al. teach antihistamines, such as pheniramines and promethazine and antitussive-expectorants, such as guaifenesin, which are

useful for their histamine-blocking and cough suppressing properties. The expected result would be an improved formulation for the treatment of cough suppression and allergic conditions.

With regards to particular amounts of active agents, the Examiner points out that generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

* * * * *

(10) Response to Argument (A):

***Note*: Independent claims 1, 27 and 68 and dependent claims 12-14 were argued separately and are addressed below:**

With respect to independent claim 1, Appellant argues, "Fanara is primarily concerned with pharmaceutical compositions for the controlled release of active substances, not with the administration of different active substances in a single dosage form."

This argument not deemed persuasive. Claim 1 is met by the disclosure of Fanara. Fanara explicitly teaches on col. 2, lines 36-50 that it is "increasingly therapeutically advantageous to be able to simultaneously administer by the oral route an active substance released immediately after administration and the same or a *second active substance* released gradually and regularly after administration". The reference clearly suggests the administration of varying active substances that can be administered simultaneously as is also desired by Appellant. See also, column 5, lines 48-58, whereby Fanara teaches a bi-layered composition comprising, "...at least one layer comprising an active substance and at least a second layer

which allows the controlled release of the same or of a *second active substance*...". Thus, the reference teaches administration of different active substances sufficiently provided in a single dosage form and reads on the limitations of instant claim 1.

Appellant argues with respect to independent claim 1, "Fanara mentions immediate release/controlled release combinations, i.e., combinations which provide different release rates of the active substances, but is completely silent with respect to the duration of action of the active substances in relation to time and duration of action of the other active substance."

This argument was not found convincing since Appellants are not claiming a specific drug release profile of the first and second active substances with respect to time, which would patentably define and distinguish over the release rates suggested by Fanara. Moreover, as noted above, Fanara employs and teaches multi-layered dosage forms comprised of various active substances and achieves therapeutically-effective results using the same. Thus, the results sought by Appellant are achieved by the prior art. Furthermore, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., duration of action in relation to time) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Hence, Appellant's arguments do not establish the scope of claims being presented.

With respect to claims 1 and 68, Appellant then argues, "Fanara does not render obvious the recitation of 'the dosage form providing a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70% of a period over which the dosage form provides a plasma concentration within a therapeutic range of

the first drug' and does not teach that the plasma half-life of the at least one further drug is shorter than the plasma half-life of promethazine by at least about 3 hours".

The Examiner was not persuaded by this argument. With respect to the claim language of instant claim 1, it is the position of the Examiner that the Fanara reference would meet these claim limitations. The Fanara reference explicitly recognizes and teaches simultaneous administration of multiple active agents whereby it is possible to combine therapeutic effects of active substances having very different pharmacokinetic profiles. With regards to claim 68, which requires that the difference in plasma half-lives of the second drug to the first drug to be at least about 3 hours, it is noted that the Fanara reference teaches similar active ingredients as claimed and thus, the difference in the plasma half-lives would be expected to be the same as that claimed herein by Appellant. For example, co-administration of Fanara's active substances, such as antihistamine (i.e., cetirizine) in combination with a decongestant (i.e., pseudoephedrine) would yield the same drug plasma parameters sought by Appellant and would yield the same plasma curve. Additionally, Appellant has not established criticality with regards to the difference in plasma half-lives of the second drug to the first drug. The prior art amply teaches providing a dosage form for the administration of various active substances that would also be capable of supplying the difference in drug plasma as claimed and would also provide for overlap or coextension of drug activity, absent a showing of evidence to the contrary.

Regarding independent claims 1, 27 and 68 Appellant further argues, "Findlay does not teach that suitable antihistamines for the composition include pheniramines and promethazine. Findlay would teach away from including promethazine as an antihistamine in a composition disclosed by Fanara."

This argument was not found convincing. The limitations of claims 1, 27 and 68 are met by the combined teachings of Fanara in view of Findlay. Findlay amply remedies the deficiency of Fanara for the teaching of the particular antihistamine – promethazine and pheniramine and

thus meets the requirement of this particular antihistamine, as is claimed in claims 1 and 27. Claim 68 requires the generic 'antihistamine'. The reference of Fanara demonstrates the general teaching that the use of such antihistamines is well known, albeit, with certain side effects. The reference teaching, nonetheless, would not deter one of ordinary skill in the art from using the particular antihistamines for their known beneficial effects, i.e., histamine antagonistic effects. Furthermore, it is common knowledge in the pharmaceutical/chemical art that, the majority of active substances, if not all, exhibit some degree of side effects in addition to the therapeutic effects with which they provide. The fact that the prior art may highlight certain side effect(s) of a particular drug (i.e., promethazine) does not render the drug any less effective for its intended use, since the benefits of employing the drug would necessarily outweigh the negative effects of the drug. Findlay additionally teaches the same antitussive/expectorant – guaifenesin as claimed by Appellant. Moreover, with regards to claim 27, which requires a bi-layered tablet, the prior art explicitly teaches multi-layered dosage formulations comprising one or more active substances whereby the first layer of active substance is provided in immediate release form and the second layer is provided in controlled release form.

Regarding independent claim 68, Appellant argues, "Neither Fanara nor Findlay mentions or addresses any plasma half-life, let alone the difference in the plasma half-lives of two drugs, which are comprised in the same dosage form."

This argument was not persuasive since, as delineated above, it is noted that the primary reference of Fanara initially teaches similar active ingredients as claimed and thus, the difference in the plasma half-lives would be expected to be the same as that claimed herein by Appellant. For example, co-administration of Fanara's active substances would yield the same drug plasma parameters sought by Appellant. The difference in the drug plasma half-lives would be the same

and would be inherent based on the teachings of the prior art which presents administration of the same active substances. The prior art would also provide for overlap or coextension of drug activity, absent a showing of evidence to the contrary.

Regarding dependent claims 12-14, Appellant argues, "Fanara and Findlay do not teach that the plasma half-life of the at least one second drug is shorter than the plasma half-life of the first drug (promethazine and/or a pharmaceutically acceptable salt thereof) by at least about 3, 4 or 6 hours respectively."

This argument was not found persuasive. As delineated above, the Fanara reference explicitly recognizes and teaches simultaneous administration of multiple active agents whereby it is possible to combine therapeutic effects of active substances having very different pharmacokinetic profiles. The Fanara reference teaches similar active ingredients as claimed and thus, the difference in the plasma half-lives would be expected to be the same as that claimed herein by Appellant. The prior art's dosage form would also be capable of supplying the difference in drug plasma as claimed and would also provide for overlap or coextension of drug activity, as is desired by Appellant.

Appellant argues, "The Examiner's conclusions with respect to Fanara are based on hindsight".

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

General rebuttal arguments made by Appellant:

Appellant argues, "The term 'pharmacokinetic profile' encompasses a wide range of properties of a drug. Appellant are unable to see why Fanara would render it obvious to use an immediate/controlled release combination for providing plasma concentrations in a therapeutic range in such a way that the therapeutically effective period of one drug overlaps at least about 70% of the therapeutically effective period of the other drug."

The Examiner was not persuaded by this argument since the limitation "over a period which is coextensive…" is vague in that it does not refer to any specific extent or duration over which the plasma concentration of the first and second active substance should overlap. Moreover, no unexpected or superior results have been observed which would accrue based on the plasma concentration limitations. In any event, the prior art vividly teaches the release of active substances, suitable for controlled release using matrix-type pharmaceutical compositions and further teaches the same class of compounds being claimed by Applicant. The claims remain generic in structure and function and thus, would still read on the teachings of Fanara.

Appellant also argues, "Fanara make it clear that their contribution to the art does not rest in the provision of dosage forms which provide immediate/controlled release of two difference active substances but rather that their invention consists in the provision of a new matrix composition for the controlled release part of the corresponding dosage forms (and primarily for single, controlled release composition), which matrix composition has certain advantages."

Appellants arguments were not found persuasive since the Examiner notes that Fanara teaches that their pharmaceutical compositions are provided in the form of tablets, of which bi-layered and multi-layered tablets are also included (col. 5, line 15 – col. 6, line 25) as well as matrix-type pharmaceutical compositions (col. 1, lines 14-16). The bi-layered and multi-layered tablets taught by Fanara would clearly read on the generic "pharmaceutical dosage form" of instant claim 1 (which presents no specific structure requirement – *i.e.*, reads on a 'matrix' or

mixture) and reads on the bi-layered tablet of instant independent claim 27 and the pharmaceutical dosage form of independent claim 68.

* * * * *

- **(B) Claims 1-24, 27-38 and 68-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fanara *et al.* (U.S. Patent No. 6,699,502) in view of Paradissis *et al.* (U.S. Patent No. 5,445,829).**

The instant invention is drawn to a pharmaceutical dosage form which comprises (a) a first drug which is at least one of promethazine and a pharmaceutically acceptable salt thereof and (b) at least one second drug, wherein the dosage form provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug.

Fanara *et al.* ('502) teach oral pharmaceutical compositions for controlled release of active substances, whereby the compositions include multi-layered formulations. The compositions can be administered in a few daily doses, ideally in a single daily dose (see column 1, lines 5-13 and Abstract). The release of active substances during oral administration can be controlled by means of matrix-type pharmaceutical compositions (col. 1, lines 14-16).

According to Fanara, it is increasingly therapeutically advantageous to be able to simultaneously administer by the oral route an active substance released immediately after administration, and the same or a second active substance released gradually and regularly after

administration. In the case where an active substance is released immediately and another active substance is released gradually, this makes it possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles (col. 2, lines 36-50).

The compositions allow regular and continuous release of active substances over periods of at least 12 hours (col. 3, lines 28-31).

The controlled release compositions can be used in combination with an immediate release pharmaceutical composition for the same or for another active substance, in a single unit intended to be administered orally (col. 2, lines 32-37).

Suitable active substances disclosed include antihistamines, analgesics, antitussives and the like (col. 4, lines 57-58). Specific active substances taught include decongestants, such as pseudoephedrine, phenylepherine, phenylpropanolamine and antitussives such as hydrocodone, codeine, morphine, their optimal isomers or pharmaceutically acceptable salts (col. 4, lines 58-67).

The pharmaceutical compositions are provided in the form of tablets, of which bi-layered and multi-layered tablets are also included (col. 5, line 15 – col. 6, line 25).

The Examples at columns 6-18 demonstrate various layered controlled release pharmaceutical compositions of the invention. For instance, Example 7 at column 12, demonstrates a double-layered tablet comprising hydrocodone bitartrate. The double layered-tablets contained 15 mg doses of hydrocodone consisting of a controlled-release layer containing a 10 mg dose of hydrocodone and an immediate-release layer containing a 15 mg dose of hydrocodone. The results showed that 35% of hydrocodone was already released after 1 hour,

which corresponds to the hydrocodone content in the immediate release layer (33.3% of the total dose). The release of the hydrocodone continued gradually and regularly (col. 12, line 24 – col. 13, line 26).

With respect to the instant claim limitation of the "dosage form providing a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70% of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug", it is the position of the Examiner that the Fanara reference meets these claim limitations. The Fanara reference explicitly recognizes and teaches simultaneous administration of multiple active agents whereby it is possible to combine therapeutic effects of active substances having very different pharmacokinetic profiles. Thus, the Fanara reference teaches an objective similar to that being claimed by Applicant.

With regards to the plasma half-lives claimed, it is noted that the Fanara reference teaches similar active ingredients as claimed and thus, the plasma half-lives would be expected to be the same as that claimed herein by Applicant.

Regarding the limitation of the 'tablet comprising a matrix with the first drug and particles which comprise the second drug', the Examiner points out that Fanara teaches the use of layered, both bi-layered and multi-layered tablets and thus, this limitation is also met by the primary reference.

Fanara *et al.* teach antihistamines (col. 4, line 58). Fanara et al. do not teach the antihistamines promethazine and chlorpheniramine and do not teach the expectorant, guaifenesin.

Paradissis *et al.* ('829) teach extended release pharmaceutical compositions containing both an immediate release formulation and an extended release formulation, whereby the compositions are preferably in the form of a tablet (see col. 1, lines 15-26). The compositions include pharmaceutically active compounds, such as antihistamines, antitussives, expectorants and decongestants (col. 3, lines 34-41). Suitable antihistamines taught include chlorpheniramine maleate and promethazine. Suitable antitussive-expectorants taught include guaifenesin (col. 4, lines 39-47).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the suitable antihistamines and antitussive-expectorants taught by Paradissis *et al.* within the formulations of Fanara *et al.* One of ordinary skill in the art would be motivated to do so with a reasonable expectation of success because Paradissis *et al.* teach pharmaceutical compositions comprising effective antihistamines, such as chlorpheniramine and promethazine and teach antitussive-expectorants, such as guaifenesin, which are known to be useful for their histamine-blocking and cough suppressing effects. The expected result would be an enhanced formulation for treating cough and allergic conditions.

With regards to particular amounts of active agents, the Examiner points out that generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

(10) Response to Argument (B):

(*Note:* Appellant's arguments with regards to "Fanara" above are the same as the arguments presented herein and are reproduced below):

Independent claims 1, 27 and 68 and dependent claims 12-14 were argued separately and are addressed below:

With respect to independent claim 1, Appellant argues, "Fanara is primarily concerned with pharmaceutical compositions for the controlled release of active substances, not with the administration of different active substances in a single dosage form."

This argument not deemed persuasive. Claim 1 is met by the disclosure of Fanara. Fanara explicitly teaches on col. 2, lines 36-50 that it is "increasingly therapeutically advantageous to be able to simultaneously administer by the oral route an active substance released immediately after administration and the same or a *second active substance* released gradually and regularly after administration". The reference clearly suggests the administration of varying active substances that can be administered simultaneously as is also desired by Appellant. See also, column 5, lines 48-58, whereby Fanara teaches a bi-layered composition comprising, "...at least one layer comprising an active substance and at least a second layer which allows the controlled release of the same or of a *second active substance*...". Thus, the reference teaches administration of different active substances sufficiently provided in a single dosage form and reads on the limitations of instant claim 1.

Appellant argues with respect to independent claim 1, "Fanara mentions immediate release/controlled release combinations, i.e., combinations which provide different release rates of the active substances, but is completely silent with respect to the duration of action of the active substances in relation to time and duration of action of the other active substance."

This argument was not found convincing since Appellants are not claiming a specific drug release profile of the first and second active substances with respect to time, which would patentably define and distinguish over the release rates suggested by Fanara. Moreover, as noted above, Fanara employs and teaches multi-layered dosage forms comprised of various active substances and achieves therapeutically-effective results using the same. Thus, the results sought by Appellant are achieved by the prior art. Furthermore, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., duration of action in relation to time) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Hence, Appellant's arguments do not establish the scope of claims being presented.

With respect to claims 1 and 68, Appellant then argues, "Fanara does not render obvious the recitation of 'the dosage form providing a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70% of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug' and does not teach that the plasma half-life of the at least one further drug is shorter than the plasma half-life of promethazine by at least about 3 hours".

The Examiner was not persuaded by this argument. With respect to the claim language of instant claim 1, it is the position of the Examiner that the Fanara reference would meet these claim limitations. The Fanara reference explicitly recognizes and teaches simultaneous administration of multiple active agents whereby it is possible to combine therapeutic effects of active substances having very different pharmacokinetic profiles. With regards to claim 68, which requires that the difference in plasma half-lives of the second drug to the first drug to be at

least about 3 hours, it is noted that the Fanara reference teaches similar active ingredients as claimed and thus, the difference in the plasma half-lives would be expected to be the same as that claimed herein by Appellant. For example, co-administration of Fanara's active substances, such as antihistamine (i.e., cetirizine) in combination with a decongestant (i.e., pseudoephedrine) would yield the same drug plasma parameters sought by Appellant and would yield the same plasma curve. Additionally, Appellant has not established criticality with regards to the difference in plasma half-lives of the second drug to the first drug. The prior art amply teaches providing a dosage form for the administration of various active substances that would also be capable of supplying the difference in drug plasma as claimed and would also provide for overlap or coextension of drug activity, absent a showing of evidence to the contrary.

Regarding independent claims 1, 27 and 68 Appellant further argues, "Findlay does not teach that suitable antihistamines for the composition include pheniramines and promethazine. Findlay would teach away from including promethazine as an antihistamine in a composition disclosed by Fanara."

This argument was not found convincing. The limitations of claims 1, 27 and 68 are met by the combined teachings of Fanara in view of Findlay. Findlay amply remedies the deficiency of Fanara for the teaching of the particular antihistamine – promethazine and pheniramine and thus meets the requirement of this particular antihistamine, as is claimed in claims 1 and 27. Claim 68 requires the generic 'antihistamine'. The reference of Fanara demonstrates the general teaching that the use of such antihistamines is well known, albeit, with certain side effects. The reference teaching, nonetheless, would not deter one of ordinary skill in the art from using the particular antihistamines for their known beneficial effects, i.e., histamine antagonistic effects. Furthermore, it is common knowledge in the pharmaceutical/chemical art that, the majority of active substances, if not all, exhibit some degree of side effects in addition to the therapeutic

effects with which they provide. The fact that the prior art may highlight certain side effect(s) of a particular drug (i.e., promethazine) does not render the drug any less effective for its intended use, since the benefits of employing the drug would necessarily outweigh the negative effects of the drug. Findlay additionally teaches the same antitussive/expectorant – guaifenesin as claimed by Appellant. Moreover, with regards to claim 27, which requires a bi-layered tablet, the prior art explicitly teaches multi-layered dosage formulations comprising one or more active substances whereby the first layer of active substance is provided in immediate release form and the second layer is provided in controlled release form.

Regarding independent claim 68, Appellant argues, "Neither Fanara nor Findlay mentions or addresses any plasma half-life, let alone the difference in the plasma half-lives of two drugs, which are comprised in the same dosage form."

This argument was not persuasive since, as delineated above, it is noted that the primary reference of Fanara initially teaches similar active ingredients as claimed and thus, the difference in the plasma half-lives would be expected to be the same as that claimed herein by Appellant. For example, co-administration of Fanara's active substances would yield the same drug plasma parameters sought by Appellant. The difference in the drug plasma half-lives would be the same and would be inherent based on the teachings of the prior art which presents administration of the same active substances. The prior art would also provide for overlap or coextension of drug activity, absent a showing of evidence to the contrary.

Regarding dependent claims 12-14, Appellant argues, "Fanara and Findlay do not teach that the plasma half-life of the at least one second drug is shorter than the plasma half-life of the first drug (promethazine and/or a pharmaceutically acceptable salt thereof) by at least about 3, 4 or 6 hours respectively."

This argument was not found persuasive. As delineated above, the Fanara reference explicitly recognizes and teaches simultaneous administration of multiple active agents whereby it is possible to combine therapeutic effects of active substances having very different pharmacokinetic profiles. The Fanara reference teaches similar active ingredients as claimed and thus, the difference in the plasma half-lives would be expected to be the same as that claimed herein by Appellant. The prior art's dosage form would also be capable of supplying the difference in drug plasma as claimed and would also provide for overlap or coextension of drug activity, as is desired by Appellant.

> Appellant also argues, "Fanara make it clear that their contribution to the art does not rest in the provision of dosage forms which provide immediate/controlled release of two difference active substances but rather that their invention consists in the provision of a new matrix composition for the controlled release part of the corresponding dosage forms (and primarily for single, controlled release composition), which matrix composition has certain advantages."

Appellants arguments were not found persuasive since the Examiner notes that Fanara teaches that their pharmaceutical compositions are provided in the form of tablets, of which bi-layered and multi-layered tablets are also included (col. 5, line 15 – col. 6, line 25) as well as matrix-type pharmaceutical compositions (col. 1, lines 14-16). The bi-layered and multi-layered tablets taught by Fanara would clearly read on the generic "pharmaceutical dosage form" of instant claim 1 (which presents no specific structure requirement – *i.e.*, reads on a 'matrix' or mixture) and reads on the bi-layered tablet of instant independent claim 27 and the pharmaceutical dosage form of independent claim 68.

> Appellant argues, "The Examiner's conclusions with respect to Fanara are based on hindsight".

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on

obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

PARADISSIS:

Appellant argues, "Paradissis, like Fanara and Findlay, is primarily concerned with extended (controlled) release formulations and as such makes it clear that combination of these extended release formulations with immediate release formulations are merely optional. Paradissis is not concerned with any overlap in the periods of therapeutic effectiveness of two drugs which are comprised in the same dosage form."

This argument was not deemed persuasive. Appellants' claims simply desire some overlapping or coextension of therapeutic activity, whereby it is noted that the prior art could also achieve this effect. The prior art explicitly teaches simultaneous administration of active ingredients. Absent a showing of evidence to the contrary, the formulations of the prior art would be capable of providing overlap of therapeutic activity between the first and second active substances. Moreover, Appellant's arguments that "extended release formulations with immediate release formulations are merely optional" in the prior art was not persuasive. Note that the instant independent claims do not address or recite either of immediate and/or controlled release. Thus, Applicant's arguments are not commensurate in scope with the claims. Furthermore, it is pointed out that Paradissis was relied upon for the teaching of the antihistamine – promethazine and thus is ample for all that it teaches and suggests.

> Appellant argues, "Paradissis fails to provide any motivation for one of ordinary skill in the art to pick and choose promethazine, a drug which is mentioned in a laundry list of exemplary drugs and which is not even included in the list of preferred drugs in the paragraph bridging columns 4 and 5."

This argument was not persuasive since Paradissis clearly teaches promethazine as one of the effective antihistamines of choice that is suitable for use in their formulation. It is of no moment that Paradissis does not place promethazine in its list of "preferred" drugs, since preferred as well as non-preferred embodiments of the reference are taken into consideration for determining grounds for obviousness. "[T]he prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed…." In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). In this instance, the reference of Paradissis clearly demonstrates that the use of such antihistamines (i.e., promethazine) in oral dosage forms would be beneficial.

Regarding independent claim 27 Appellant argues, "Fanara in view of Paradissis does not provide for a dosage form which releases any two different drugs in such a way that the therapeutically effective period of one drug overlaps the therapeutically effective period of the other drug by at least about 70%."

The Examiner was not persuaded by this argument. It is the position of the Examiner that these instant claim limitations are sufficiently met by the prior art of record. A review of the instant specification establishes that the plasma concentration (of promethazine) being within a therapeutic range for at least about 24 hours per single dose is achieved as a result of the use of layered (i.e., bi-layered) dosage formulations having varied release rates (i.e., immediate release, controlled release). The prior art applies the same technique as that of the instant invention. Namely, the prior art of record explicitly teaches multi-layered dosage formulations comprising

one or more active substances whereby the first layer of active substance is provided in immediate release form and the second layer is provided in controlled release form. See for instance, Example 7 at column 12 of Fanara, which amply demonstrates a double-layered tablet comprising hydrocodone bitartrate. The double layered-tablets contained 15 mg doses of hydrocodone consisting of a controlled-release layer containing a 10 mg dose of hydrocodone and an immediate-release layer containing a 15 mg dose of hydrocodone. Thus, the prior art vividly recognizes and teaches the use of multi-layered dosage forms which deliver active agents in both immediate as well as controlled/sustained release. Since this same technique is utilized by the prior art to provide for effective therapeutic effects, as is desired by Appellant, it cannot be seen as to how the prior art would not obtain an effective plasma concentration of a drug. The Fanara reference explicitly recognizes and teaches simultaneous administration of multiple active agents whereby it is possible to combine therapeutic effects of active substances having very different pharmacokinetic profiles.

Regarding independent claim 68, Appellant argues, "Neither Fanara nor Paradissis mentions or addresses any plasma half-life, let alone the difference in the plasma half-lives of two drugs, which are comprised in the same dosage form."

This argument was not persuasive since, as stated above, it is noted that the primary reference of Fanara initially teaches similar active ingredients as claimed and thus, the difference in the plasma half-lives would be expected to be the same as that claimed herein by Appellant. For example, co-administration of Fanara's active substances would yield the same drug plasma parameters sought by Appellant. The difference in the drug plasma half-lives would be the same and would be inherent based on the teachings of the prior art which presents administration of

the same active substances. The prior art would also provide for overlap or coextension of drug activity, absent a showing of evidence to the contrary.

Lastly, regarding dependent claims 12-14, Appellant argues, "Fanara and Findlay do not teach that the plasma half-life of the at least one second drug is shorter than the plasma half-life of the first drug (promethazine and/or a pharmaceutically acceptable salt thereof) by at least about 3, 4 or 6 hours respectively."

This argument was not deemed convincing. The prior art of record (Fanara) teaches simultaneous administration of multiple active agents whereby it is possible to combine therapeutic effects of active substances having very different pharmacokinetic profiles. The Fanara reference teaches active ingredients as claimed and thus, the difference in the plasma half-lives would be expected to be the same as that claimed herein by Appellant. The prior art's dosage form would also be capable of supplying the difference in drug plasma as claimed and would also provide for overlap or coextension of drug activity, as is desired by Appellant.

In view of the teachings of the art supplied above, the instant invention would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made, based on the combined disclosure of Fanara in view of Findlay and Fanara in view of Paradissis.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Humera N. Sheikh/

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